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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/241,595	02/02/99	REIMANN J	9325-0008.30

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EXAMINER	
BECKERLEG, A	
ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 08/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/241,595	REIMANN ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/20/01,05/03/01 and 05/21/01* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's responses received on 3/20/01, 5/3/01, and 5/21/01 have been entered. Claims 1-30 are pending in the instant application. An action on the merits follows.

The text of those sections of Title 35, US code, not included in this office action can be found in the previous action, paper no. 6.

Claim Rejections - 35 USC § 112

The rejection of claims 1-5, 7-8, 10-13, 16-17, 20-21, 23, and 25-30 for lack of written description under 35 U.S.C. 112, first paragraph, is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that aside from the proteins disclosed in the specification, oligodeoxynucleotides (ODNs) were known in the art as adjuvants for stimulating immune responses and as such the skilled artisan would have recognized their usefulness in the instant invention. In support of this argument the applicant provides a post-filing publication demonstrating the inclusion of an ODN in HBsAg particles. While the applicant states that ODNs were known in the literature, the literature did not report their use in vaccination in combination

with HBsAg particles or disclose that ODNs could be encapsulated by HBsAg particles. The specification is completely silent in regards to the characteristics of any ODN and provides no description or guidance for their inclusion in HBsAg particles. Further, Schirmbeck et al. (identified by the applicant as Reimann et al. on page 4 of the response received on 3/20/01) was published after the filing of the instant application and teaches ODNs and methods of incorporating ODNs which were not known at the time of filing or taught by the specification. Thus, the teachings of this article cannot be used to demonstrate the common knowledge of the skilled artisan prior to the filing of the instant application. Therefore, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for biologically active molecules which are not proteins.

The rejection of claims 1-30 under 35 U.S.C. 112, first paragraph, for lack of enablement is maintained in part. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

As noted in the previous office action, the claims directed to compositions comprising the HBsAg particles containing a biologically active molecule are included in this rejection in terms of "how to use" the molecules according to the disclosure of the specification. In addition, it is noted that in regards to the methods of stimulating an immune response, the specification clearly teaches that the purpose of stimulating an immune response is for vaccination against infectious organisms

such as viruses or bacteria (specification page 2). The specification does not provide any reason for stimulating any immune response using the disclosed particles other than for protecting or treating infection.

The applicant argues that the term "encapsulation" encompasses both the noncovalent inclusion of a biologically active molecule in the interior of the particles **or** the exposure or presence of the molecule at the surface of the particle such that the molecule does not necessarily penetrate into the interior of the particle (applicant's response, page 6). In view of this definition of the term "encapsulation", it is acknowledged that the specification is enabling for making HBsAg particles which contain a hydrophobic protein or peptide, wherein the hydrophobic protein or peptide is incorporated into or attached to the HBsAg particle surface. It is noted, however, that applicants have not presented any arguments or evidence refuting the lack of enablement for making HBsAg particles which contain non-covalently and non-chemically coupled hydrophobic proteins or peptides in the interior of the HBsAg particles.

The applicant argues that the specification provides sufficient guidance for routes and dosages of the instant particles and that several publications available in the art at the time of filing teach vaccination with HBsAg particles citing Bohm et al. (referred to as Reimann et al.), Ellis et al., Woodrow et al., and Ellis. However, all of these publications are limited to the administration of unmodified HBsAg particles which do not contain a biologically active molecule according to the instant invention for the purpose of stimulating immune responses against the HBsAg antigen itself in order to vaccinate against hepatitis B. None of these references teach the level of non-

HBsAg antigen concentration, dosage of non-HBsAg antigen containing HBsAg particles, or routes of modified particle delivery that result in the generation of enhancement of CTL or antibody responses against the incorporated non-HBsAg antigen, particularly in the circumstance where the non-HBsAg antigen by itself is ineffective in generating a CTL response. It is further noted that the unmodified HBsAg particles taught in the provided publications are clearly capable of generating immune responses in the absence of any additional immunostimulatory molecule. Thus, while the provided publications demonstrate the induction of anti-HBsAg immune responses using unmodified HBsAg particles, a nexus cannot be drawn between the use of the unmodified particles taught in these publications and the modified HBsAg particles disclosed in the specification.

The previous office action discussed in detail the parameters affecting the generation of different types of immune responses and the unpredictability of whether any level of any type of immune effector response against a particular antigen would correlate with a therapeutic effect on any disease associated with the immunizing antigen (Abbas et al., Golding et al., Yasumtomi et al., and Fox). The applicant argues that the specification deals with the stimulation or modulation of MHC class I restricted CTL responses. However, applicant's claims are broad and read on the stimulation or modification of any type of immune response (see claims 1, 5-11, and 14-16). Thus, the ability of the compositions to induce other types of immune responses besides a CTL response is a relevant issue to the enablement of the instant claims.

In regards to the encapsulation of cytokines, the applicant argues that the specification discloses the successful use of IL-12 and IFN-gamma and that IL-2 may represent an inoperative species within the genus of immunostimulating molecules which would not preclude enablement for the broad claims. However, as discussed in the previous office action, the genus of immunostimulating molecules is extremely broad and includes not only numerous cytokines with highly disparate functions, but also bacterial adjuvants and ODNs whose activity is unrelated to the activity of IL-12 or IFN-gamma. Of the numerous species encompassed by the term immunostimulatory molecule, the specification does not provide sufficient guidance as to which cytokines, bacterial antigens, or ODNs would be capable of stimulating any type of immune response including a CTL response. Further, the failure of IL-2 to stimulate a CTL response is important, as of the many known cytokines, IL-2 has been reported in the prior art to have CTL stimulating activity. Thus, the applicant's demonstration that IL-2, a known CTL stimulating cytokine, is ineffective in the instant particles and methods of stimulating CTL increases the unpredictability of determining what other cytokines, particularly those without known CTL stimulating activity, would be capable of achieving the desired result. It is noted that we agree with the district court's conclusion on enablement. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude * * * possible inoperative substances * * * *" In re Dinh-Nguyen, 492 F.2d 856, 858-59, 181 USPQ 46, 48 (CCPA 1974) (emphasis omitted). Accord, In re Geerdes, 491 F.2d 1260, 1265, 180 USPQ 789, 793 (CCPA 1974); In re Anderson, 471 F.2d 1237, 1242, 176

USPQ 331, 334-35 (CCPA 1973). Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

In regards to the immunization against HBV or HIV, the applicants have provided several publications which are reputed to provide a correlation between CTL generation and immunization with HIV or HBV antigens. These papers demonstrate the induction of anti-HBV or anti-HIV specific CTL following a variety of different immunization strategies that are not related to the instant methods which involve the administration of modified HBsAg particles. The ability of HBV or HIV antigens to stimulate a CTL response in not at issue. The previous office action states that the specification does not provide an enabling disclosure for immunization against HBV or against diseases associated with antigen encapsulated by the HBsAg particles of the instant invention. The specification clearly discloses that the purpose of generating an immune response using the disclosed particles is for vaccination against disease, in particular HIV and HBV. However, the specification does not provide any guidance or experimental data which correlates the observed level of CTL response generated against HIV/env/V3 in mice administered HIV/env/V3 encapsulated in HBsAg particles, or against HBsAg in mice administered HBsAg particles encapsulating IL-12, y-IFN, cholera toxin or enterotoxin, with any effect on HIV or HBV infection. The art at the time of filing teaches that the strength and character of an immune response to a particular antigen or epitope significantly effects the ability

of the host to successfully protect against or ameliorate disease or infection. (see Yasumtomi et al., and Fox). Thus, in view of the art recognized unpredictability of vaccinating against HIV, the lack of correlation between the applicant's CTL data and any effect on HIV or HBV infection, and the breadth of the claims, the skilled artisan would not have predicted success in vaccinating any mammal against any disease by administering HBsAg particles encapsulating a disease antigen and/or immunostimulatory molecule.

Prior Art

The previous office action stated that the term "contained in" was being interpreted as meaning "encapsulating" such that molecules or antigens "contained in" an HBsAg particle would not be covalently or chemically attached to the particle. However, the applicant has clearly stated on page 6 of the response received on 3/20/01 that the term "encapsulating" may be defined as including the incorporation of molecules into the exterior of the particles such that the molecules do not necessarily penetrate the interior of the particle. As such, the claims are no longer considered free of the prior art of record and the following new grounds of rejection of the claims apply.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-6, 11, 17-18, 25-27, and 29-30 are newly rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,039,522 (8/13/91), hereafter referred to as Neurath. The applicant claims a composition comprising HBsAg particles which contain a biologically active molecule, methods of incorporating a biologically active molecule into HBsAg particles by incubating the biologically active molecule with HBsAg in aqueous media, and methods of stimulating an immune response to an antigenic molecule or HBsAg by administering to a subject a composition comprising an antigenic molecule or immunostimulatory molecule contained in an HBsAg particle. The applicant further claims said compositions and methods wherein the biologically active molecule is an antigen or immunostimulatory molecule, and wherein the composition further comprises a glycolipid incorporated into the exterior of the HBsAg particle . As stated above, the applicant has defined the term "contained in" as including the inclusion of the biological molecule in the exterior of the HBsAg particle.

Neurath teaches that it is possible to add any peptide with a hydrophobic tail to HBsAg particles to produce an immunogen useful for generating immune responses against viral proteins or peptides (Neurath et al., column 3, lines 39-51). Neurath further teaches that the peptide can be a naturally occurring or synthetic peptide derived from HIV or hepatitis B (Neurath, column 3,

lines 46-62). Neurath also teaches the preparation of HBsAg particles which contain myristolated hepatitis B preS antigen by incubating myristolated preS protein with HBsAg in an aqueous media (Neurath, column 10, lines 13-48). In addition, Neurath teaches the immunization of rabbits with the preS containing HBsAg particles resulting in the generation of anti-HBV antibodies (Neurath, column 9-51). It is noted that antigens are inherently considered immunostimulatory molecules as their expression results in the generation of immune responses. Thus, by teaching all the limitations of the claims, Neurath anticipates the instant invention.

Claims 1-2, 5-7, 11-12, 17-19, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Michel et al. (1993) Res. Virol. Vol. 144, 263-267. The applicant claims a composition comprising HBsAg particles which contain a biologically active molecule, and methods of stimulating an immune response to an antigenic molecule or HBsAg by administering to a subject a composition comprising an antigenic molecule or immunostimulatory molecule contained in an HBsAg particle. The applicant further claims said compositions and methods wherein the biologically active molecule is an antigen or immunostimulatory molecule, such as the HIVenv/V3 peptide, and wherein the immune response is a CTL response.

Michel et al. teaches the production of HBsAg particles which incorporate a hybrid HIVenv/V3 peptide in the exterior of the particles (Michel et al., page 264, column 2). It is noted that the HIV env/V3 peptide contains CTL epitopes as well as antibody and helper T cell epitopes and includes an epitope capable of binding to murine Kd. Immunization of macaques with the

hybrid HIV/HBsAg particles resulted in anti-HIV and anti-HBsAg antibodies and CTL (Michel et al., page 266). Thus, by teaching all the elements of the claims, Michel et al. anticipates the instant invention.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER